ARTICLE IN PRESS

Best Practice & Research Clinical Obstetrics and Gynaecology xxx (2012) 1–13

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

1

Overview of microbicides for the prevention of human immunodeficiency virus

Salim S. Abdool Karim, MBChB, PhD, Professor [a,b,*], Cheryl Baxter, MSc, Mrs [a]

[a] CAPRISA – Centre of AIDS Programme of Research in South Africa, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag X7, Congella 4013, Durban, South Africa
[b] Department of Epidemiology, Columbia University, NY, New York, USA

Keywords:
HIV
women
microbicide prevention

Human immunodeficiency virus (HIV) prevention tools that women can use and control are urgently needed. Microbicides are chemical products applied to the vagina or rectum to prevent the sexual transmission of HIV. Four classes of candidate microbicides have been tested to date: those that (1) enhance the natural defences in the vagina to inactivate HIV; (2) inactivate HIV in the vagina; (3) prevent HIV from attaching to, and fusing with, the host cells; and (4) prevent HIV from replicating in genital tract host cells. Despite numerous disappointing efficacy trial results over the past 20 years, substantial progress is now being made in microbicide development after the release of the CAPRISA 004 trial, which provided proof-of-concept that topical antiretroviral microbicides can prevent sexual transmission of HIV and herpes simplex type-2 infection. Microbicides, which fill an important gap for women-controlled prevention methods, have the potential to alter the course of the HIV pandemic.

Women and human immunodeficiency virus

Nearly one-half of the 33.4 million people living with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) worldwide are women.[1] In sub-Saharan Africa, women account for 59% of all infected adults. Young women are especially vulnerable. Worldwide,

* Corresponding author. CAPRISA - Centre of AIDS Programme of Research in South Africa, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag X7, Congella 4013, Durban, South Africa. Tel.: +27 31 260 4550; Fax: +27 31 260 4549.
E-mail address: karims1@ukzn.ac.za (S.S. Abdool Karim).

1521-6934/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bpobgyn.2012.01.010

60% of people aged 15–24 years with HIV are women, and between 70 and 90% of all HIV infections among women are caused by heterosexual intercourse. In sub-Saharan Africa, women aged 15–24 years with HIV represent 76% of the total cases in that age group, outnumbering their male peers by three to one.[2,3]

Why a women-controlled prevention option for human immunodeficiency virus?

Many factors make women more vulnerable than men to acquiring HIV during sex. These include biological factors,[4–6] sexual coupling patterns, where young women partner with older men who are more likely to be infected,[7] multiple concurrent relationships,[8] low marriage rates,[9] low consistent condom use rates,[10,11] and limited skills in negotiating safer sex practices. Gender-based violence[12] and poverty also increase a woman's vulnerability for acquiring HIV infection.[13] Despite the greater vulnerability of women, current HIV-prevention strategies provide little protection for women, especially young women, who can rarely negotiate condom use or faithfulness with their male partners. The female condom has been marketed as an alternative barrier method, but this device, like the male condom, also requires acceptance by the male partner. New technologies that women can use and control to prevent the sexual transmission of HIV in women are clearly needed.

What are microbicides?

Microbicides are chemical products that are self-administered prophylactic agents that can be applied topically in the vagina or rectum as a single agent or multi-component strategy. They are one of the most promising technologies under development to reduce the risk of sexual acquisition of HIV. Their purpose is to prevent, or at least significantly reduce, the acquisition and transmission of HIV (and possibly other sexually transmitted infections) at the genital (vaginal, penile or both), gastrointestinal (rectal) mucosa, or both.

In this chapter, we describe the different mechanisms of action of microbicides, the classes of candidate microbicides tested to date, the current state of clinical development of microbicides, the obstacles to the development of microbicides, and the future for microbicides.

Mechanisms of action of microbicides

The principal target of microbicides in women is to reduce acquisition (i.e. male-to-female HIV transmission), although they could potentially prevent onward (i.e. female-to-male) transmission. Candidate microbicides use one or more of the following mechanisms of action to combat infection: (1) they can support normal vaginal defences (buffers); (2) destroy surface active pathogens by disrupting membranes (surfactants); (3) inhibit pathogen entry into mucosal cells by creating a barrier between the pathogen and the vagina (blockers); (4) prevent fusion between the membranes of the pathogen and mucosal cells (inhibitors); and (5) inhibit a virus from replicating once it has infected the cells that line the vaginal wall (replication inhibitors). Examples of microbicide candidates capable of these actions are presented in Table 1. Most of microbicide candidates in late-stage development are formulated with antiretroviral (ARV) drugs that inhibit viral replication.

Classes of candidate microbicides tested to date

Buffers

A microbicide could be used to supplement or enhance the natural immune defenses of the vagina. Combinations of microbiological, chemical, and physical barriers act to protect the vagina naturally from infection. The vagina is usually maintained at a low pH of about 4. This low pH is achieved through the secretion of lactic acid by the lactobacilli, which occur naturally in the vagina. These lactobacilli are sometimes destroyed by intercurrent vaginal infections (e.g. bacterial vaginosis). A disruption of the natural balance of the vaginal ecosystem enhances the risk of HIV infection.

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

Table 1
Mechanism of action of candidate microbicides.

	Action	Examples of candidate microbicides
1.	Maintenance or mobilisation of normal vaginal defences	Buffergel®; engineered *lactobacillus*; hydrogen peroxide and peroxidises.
2.	Destroying surface active pathogens by disrupting membranes	Nonoxynol-9 and octoxynol-9; benzalkonium chloride; C31 G – SAVVY® chlorhexidine zinc gel.
3.	Inhibiting pathogen entry into mucosal cells	Carraguard®/PC-515; PRO2000® gel; Emmelle™ and dextrin-2–sulphate.
4.	Preventing fusion between the membranes of the pathogen and mucosal cells	Maraviroc (CCR5 inhibitor); soluble CD4.
5.	Inhibiting post-fusion replication (poorly absorbed antiretroviral agents)	Tenofovir (nucleotide reverse transcriptase inhibitor). Dapivirine (non-nucleoside reverse transcriptase inhibitor).

The naturally low pH of the vagina is affected substantially by semen, which is alkaline and can result in the loss of this barrier to pathogens. Microbicides have been developed to maintain the colonisation of the vagina by lactobacilli or to recolonise the vagina with lactobacilli when these commensal organisms have been adversely affected (e.g. by the use of antibiotics or genital tract infections). The candidate microbicide, Buffergel®, which acts as a pH buffer, was not shown to alter the risk of HIV infection when evaluated in a phase III effectiveness trial.[14] Research into other candidates that maintain or enhance vaginal defenses is continuing. For example, the use of a live recombinant *Lactobacillus, L. jensenii*, has been shown to reduce simian HIV transmission by 63% in a repeat challenge macaque model.[15]

Surfactants

Surfactants act by inactivating pathogens, including HIV, while they are in the lumen of the vagina. These products have a wide spectrum of activity against several microbes and spermatozoa. They disrupt cell membranes or, in some instances, change the cell's membrane structure to make it more porous and thereby more liable to disruption. The best known product in this category is nonoxynol-9, which had been widely available as a spermicide for many years. Various doses and formulations of nonoxynol-9 were tested,[16] including the sponge,[17] film[18] and gel,[19] but none were shown to prevent acquisition of HIV. Several years later, another surfactant, SAVVY® (C31 G), was tested in Ghana and Nigeria, but these studies also did not find any significant effect on HIV prevention.[20,21] Surfactants are no longer considered a viable option as a microbicide.

Blockers

This category of candidate microbicides includes the polyanionic sulfated or sulphonated polymers that had a more limited spectrum of activity. The envelope of HIV, particularly the gp41 component, which enables fusion with the cell membrane, is considered a critical target for preventing HIV infection. Compounds such as PRO 2000®, Carraguard®, cellulose sulfate, and dextrin 2-sulfate, have been evaluated as potential microbicides because of their ability to prevent the virus from attaching to, and fusing with, the host cells. Despite compelling evidence of activity against HIV *in vitro* and in animal studies,[22–28] none of these products were shown to prevent HIV in large scale human trials.[14,29,30]

Antiretroviral agents

Several antiretroviral drugs, which were originally developed as HIV therapeutics, are now being tested as potential microbicides because of they can inhibit viral replication. These antiretroviral agents

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

can act either locally in the reproductive tract mucosa or systemically at specific steps in the HIV replication cycle, and therefore have a narrow spectrum of activity against HIV only. Tenofovir gel, developed by Gilead Sciences, was recently shown to prevent sexually acquired HIV infection in women.[31]

Two non-nucleoside reverse transcriptase inhibitors, dapivarine (TMC-120) and UC781 are also being evaluated as candidate microbicides. UC781 is being developed by CONRAD. Although UC781 was found to be well tolerated and safe in women and men in early clinical studies, further research on this candidate has been put on hold because of difficulties encountered with formulating UC781 in alternative dosage forms (e.g. rings and films) and in combination with tenofovir. Dapivarine is being developed by the International Partnership for Microbicides in two dosage forms: a monthly vaginal ring and a once-daily gel.

Antiretroviral candidates are also being evaluated in combination with other products (e.g. MIV150 in combination with Carraguard®).

Co-receptor blockers

Another critical step in the HIV life cycle is the binding of HIV to chemokine co-receptors such as CCR5 or CXCR4 on the cell surface. Thus, molecules that are capable of attaching to these co-receptors and thereby preventing them from attaching to the cell surface may also be potentially effective vaginal microbicides. This is the mechanism of action of the co-receptor blocker, PSC-RANTES, which has been shown to provide protection in vaginal challenge studies in rhesus macaques without causing detectable toxicity or histological changes.[32] Rhis requires high doses of PSC-RANTES, however, which are expensive using current technology. In addition, resistant isolates to some CCR5 inhibitors have already been described.[33] The most valuable type of co-receptor blocker candidate microbicide will be one that is capable of acting against diverse strains of HIV. One such molecule, C34, a 34-residue peptide of gp41, is a promising candidate and it is a broad spectrum, highly potent inhibitor of envelope-mediated cell fusion over the entire panel of HIV-1 and simian immunodeficiency virus (envelope glycoproteins), which suggests that C34 may be a promising therapeutic against diverse or resistant strains of HIV-1.[34]

Rectal microbicides

The mucosal surfaces in the rectum are vulnerable to physical damage during sex and potentially increase the risk of HIV infection. It is a common misconception that anal intercourse is an exclusively homosexual male practice, not only in Africa but throughout the world.[35] Several surveys indicate that heterosexual anal intercourse is far more common than generally acknowledged.[36–39] Women who engage in anal intercourse may be less likely to use condoms and more likely to engage in risky behaviours.[38] In some settings, unprotected anal intercourse is viewed as an alternative to vaginal sex to preserve virginity in young women. In countries in Africa where female genital mutilation (female circumcision) is practised, anal intercourse is often experimented with during the weeks and months before painless vaginal penetration can be achieved.

Men who have sex with men (MSM) have been largely ignored in HIV prevention and treatment efforts in Africa. A pattern is emerging of increasing transmission of HIV in African MSM, with HIV prevalence rates ranging from 10.6% in Kenya to 33% in Zambia.[40] A particularly high-risk subgroup, with over 60% unprotected anal intercourse, is the rapidly growing group of MSM sex workers, mainly in the big cities in Africa. Clearly, rectal microbicides are needed in a high-risk population like MSM and female sex workers, but further research on the role of anal sex in HIV acquisition in women in the general population in Africa is urgently required.

It is possible that vaginal microbicide products may also be beneficial if used rectally in both men and women. There are distinct structural differences, however, between the vagina and rectum, and little is known about the necessary rectal mucous membrane coating required to prevent HIV. With some candidate microbicide products, specific vaginal and rectal formulations are available, such as a low osmolality tenofovir gel that has been specifically formulated for rectal use. Clinical trials evaluating the safety and effectiveness of rectal microbicides are under way.

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

Formulations: sponges, films, gels and rings

Effective microbicides will probably be delivered in many forms, such as gels, creams, suppositories, films, sponges and vaginal rings. Many microbicidal products are in various stages of development, but testing the efficacy and safety of microbicides involves many thousands of women over several years. The number of topical microbicide candidates in development (pre-clinical and clinical) in the past 10 years has averaged between 50 and 60 products; however, only one, tenofovir gel, has been shown to prevent HIV.

Current state of clinical development of microbicides

A women-initiated HIV prevention strategy was first proposed more than 2 decades ago.[41] Since then, several candidate microbicides have entered effectiveness trials to assess their effect on the prevention of HIV infection.

The first microbicide gels to enter phase III trials were surfactants, nonoxynol-9 and SAVVY®(C31-G), but both failed. The definitive trial of nonoxynol-9 among sex workers in Benin, Côte d'Ivoire, South Africa, and Thailand showed that nonoxynol-9 increased the risk of HIV infection among women who used the product more frequently, possibly owing to an increased frequency of epithelial disruption.[19] SAVVY®, however, which was tested in two separate studies in Ghana and Nigeria, showed no significant effect on HIV prevention, primarily as a result of lower than expected HIV incidence rates in the targeted population.[20,21]

Studies of the polyanions, including cellulose sulphate, Carraguard®, and PRO 2000®, conducted between 2007 and 2009, also failed to show any significant effect on HIV acquisition. The cellulose sulphate trial conducted in several African countries and a site in India was stopped prematurely because of safety concerns. Interim analysis suggested that the product may have increased the risk of acquiring HIV. Final analysis suggested no effect on HIV acquisition.[30] Carraguard was also shown to have no effect on HIV.[29] In 2009, there was a small glimmer of hope in the HPTN 035 study, which showed that 0.5% PRO 2000® reduced HIV infection by 33%, although the results were not statistically significant.[14] Subsequent findings from the almost three-fold larger MDP 301 trial,[42] which had 0.5% PRO 2000® and placebo groups comprising 6268 women with 253 HIV infections, showed that 0.5% PRO 2000 had no protective effect against HIV infection (risk ratio: 1.05).

BufferGel®, designed to maintain a healthy vaginal milieu, was also tested alongside 0.5% PRO 2000® in the HPTN 035 trial, but no effect on HIV acquisition was detected.[14]

Given the disappointing clinical trial results with surfactants, and buffering agents, these candidates have essentially disappeared from the product development pipeline.

The clinical development pathway is currently dominated by antiretroviral agents (Fig. 1).[43] The first antiretroviral agent to be tested as a potential microbicide was tenofovir gel, which is also the only microbicide candidate that has been shown to prevent HIV.[31] Tenofovir, an adenosine nucleotide analog with potent activity against retroviruses,[44] was initially developed and tested as a prophylactic in monkeys, and was subsequently formulated for oral use as tenofovir disoproxil fumarate (Viread®), which is now widely used for HIV treatment. Tenofovir's efficacy in suppressing viral replication, favourable safety profile and long half-life,[45] made it an ideal choice as the first antiretroviral drug to be formulated as a microbicide gel.

In 2010, the CAPRISA 004 tenofovir gel trial[31] showed that tenofovir gel, applied before and after sex, reduced HIV incidence by 39% (95% confidence interval 6 to 60) overall and by 54% in women who used the gel consistently. This trial provided proof-of-concept that an antiretroviral agent can prevent sexual transmission of HIV in women and has provided the first evidence that tenofovir gel is a safe and effective microbicide.

In 2011, the Microbicide Trial Network's VOICE study,[46] which was examining the safety and effectiveness of 1% tenofovir gel and two oral antiretroviral agents (tenofovir (TDF) and emtricitabine (FTC-TDF)) taken daily to reduce the risk of HIV acquisition in women, announced that the tenofovir tablet and tenofovir gel arms were to be halted because interim results showed that they were no better than placebo in preventing HIV in the study women.[47,48] These results are perplexing as there is good evidence from laboratory research, animal studies and human trials showing that tenofovir gel

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

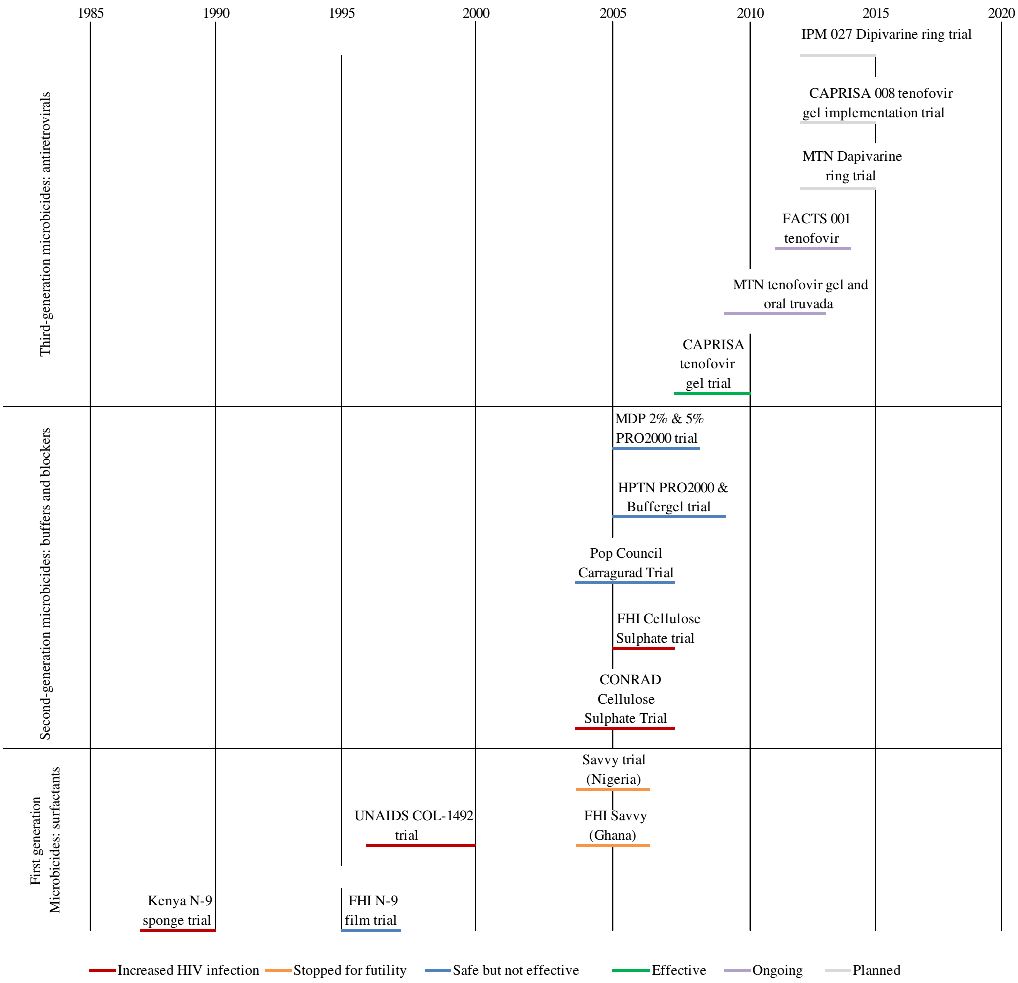

Fig. 1. Past and current microbicide effectiveness trials. Adapted with permission.[43]

prevents HIV. A detailed systematic examination of the VOICE study data, which is planned to take place in late 2012, will be needed to understand the reason for the results.

In the meantime, another placebo-controlled study, the Follow-on African Consortium for Tenofovir Studies 001 (FACTS 001),[49] is continuing to confirm and extend the findings of the CAPRISA 004 trial[31]. The FACTS 001 trail, which is testing tenofovir gel using the same BAT24 coitally related dosing regimen as the CAPRISA 004 trial[31] in 18–30-year olds could provide valuable data needed for regulatory approval.

If proven effective, tenofovir gel has the potential to alter the course of the HIV epidemic. In South Africa alone, it is estimated that, over the next 2 decades, this gel could avert 1.3 million new HIV infections and over 800,000 deaths.[50] Implemented on a broader scale, tenofovir gel could save millions of lives over time.

In preparation for the implementation of tenofovir gel into the public health service, CAPRISA is planning to undertake an implementation study (CAPRISA 008) in the communities where the CAPRISA 004[31] trial took place. Trial participants and other women from the study communities will be

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

invited to enrol in this study, which aims to address critical implementation questions about how best tenofovir gel could be incorporated into current health systems and made accessible to women who would benefit most from this product while also providing a mechanism for ongoing post-trial access to the tenofovir gel in these communities.

In addition to the clinical trials of tenofovir, a number of trials have assessed another antiretroviral drug, dapivirine (TMC-120), formulated as a vaginal gel and a vaginal ring, and some early human studies on two other classes of microbicides. These include: Amphora™ gel,[51] a barrier and vaginal defense enhancer, and VivaGel™, an entry and fusion inhibitor. Unfortunately, in addition to these candidates, no products are likely to enter phase IIb and phase III trials in the near future. Current and planned clinical trials of topical microbicide candidates are summarised in Table 2.[52]

Current state of preclinical development of microbicides

Over 70 microbicides candidates are in the preclinical development pipeline. These include 35 attachment, fusion, and entry inhibitors, 10 replication inhibitors, one vaginal defense enhancer, one immunomodulator, and four with uncharacterised mechanisms of action.[43] Early developmental research is also starting to focus on candidates with multiple mechanisms of action (Table 3).[43] The development of these candidates, however, is more complex, as each component of the combination may have to demonstrate effectiveness to warrant inclusion in a combination product.

Table 2
Ongoing and Planned Clinical Trials of Topical Microbicide Candidates (January 2012).

Phase	Trial name	Candidate(s)	Mechanism of action	Location	Population
IIIb	CAPRISA 008	Tenofovir gel	Replication inhibitor	South Africa	700 women planned
III	MTN020	Dapivirine vaginal ring	Replication inhibitor	Malawi, South Africa, Uganda, Zambia, Zimbabwe	3476 women planned
	IPM 027	Dapivirine vaginal ring	Replication inhibitor	Kenya, Malawi, South Africa, Rwanda	1650 women planned
	FACTS 001[49]	Tenofovir gel	Replication inhibitor	South Africa	2200 women
IIb	VOICE[46]	Tenofovir gel; Oral TDF/FTC[a]	Replication inhibitor	Malawi, South Africa, Uganda, Zimbabwe	5000 heterosexual women
II	MTN 017	Reformulated tenofovir gel for rectal use	Replication inhibitor	Peru, South Africa, Thailand, United States	216 men who have sex with men planned
I/II	IPM 015[53]	Dapivirine vaginal ring	Replication inhibitor	South Africa, Kenya, Malawi, Rwanda, Tanzania	280 women
	IPM 014A[54]	Dapivirine vaginal gel	Replication inhibitor	Kenya, Malawi, Rwanda, South Africa	320 women
	IPM 014B[54]	Dapivirine vaginal gel	Replication inhibitor	South Africa	320 women
	IPM 020[55]	Dapivirine vaginal gel	Replication inhibitor	United States	180 women
I	AF 020[51]	Amphora™ /ACIDFORM™ gel	Barrier/Maintenance of normal vaginal defences	United States	36 women
	MTN 012/IPM 010[56]	Dipivarine vaginal gel	Replication inhibitor	United States	48 men
	MTN 013/IPM 026[57]	Dapivirine and miraviroc vaginal ring	Replication inhibitor	United States	48 women
	MTN 007[58]	Reformulated Tenofovir gel for rectal use	Replication inhibitor	United States	63 women and men
	Project gel[59]	Tenofovir gel	Replication inhibitor	US, Puerto Rico	240 MSM

Adapted from the Global Advocacy for HIV prevention tables on ongoing and planned clinical trials – http://www.avac.org/ht/d/sp/i/3512/pid/3512.

[a] Note the tenofovir gel, and oral TDF arms in this study were prematurely halted for futility. The FTC arm is continuing.

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

Table 3
Microbicide candidates in preclinical development. Adapted with permission.[43]

Mechanism of action	Candidates in pre-clinical development	
Vaginal defense Enhancers	Unipron	
Attachment, fusion, and entry inhibitors	5P12-RANTES	Nanobodies™
	Actohivin	Optimised dendrimers
	C52L	PEHMB
	CADA (cyclotriazadisul fonamides)	PIE 12 trimers
	Cyanovirin-N (CV-N) (including bioengineered Lactobacillus expressing CV-N)	PPCM (polycarboxylated aryl oligomer,poly[1,4-phenylene-(1-carboxyl)methylene])
		PSC-RANTES
	CMPD167	RANTES peptides (including bioengineered Lactobacillus expressing RANTES)
	D-peptides	
	DS001/ L-860,167	REP 9C, REP 9AC
	DS003/BMS-599793	Retrocyclins (RC101)
	DS004/L-860,872	sCD4-17b
	DS005/L-860,882	Single-chain ICAM
	DS007/L′644 peptide	Sodium rutin sulfate (SRS)
	EBd peptides	Soluble DC-SIGN
	Flavonoids (EGCG)	Syndecan
	Griffithsin	T1249
	ISIS 5320	Talactoferrin
	K5-N, OS(H), K50SH	
	LMBL (Lactobacillus mannose-binding lectin)	
	Maraviroc	
Replication inhibitors	Dapivirine (non-nucleoside reverse transcriptase inhibitor)	Raltegravir (integrase inhibitor)
		Ritonavir (protease inhibitor)
	Darunavir (protease inhibitor)	Saquinavir (protease inhibitor)
	EFdA (nucleoside reverse transcriptase inhibitor)	Tenofovir (nucleotide analog reverse transcriptase inhibitor)
	GS9160 (integrase inhibitor)	
	Lopinavir (protease inhibitor)	
	MIV-150 (non-nucleoside reverse transcriptase inhibitor)	
Immunomodulators	Glycerol monolaurate (GML)	
Combinations /multiple mechanisms	Dapivirine and DS003	Opuntia spp (Osp)
	Dapivirine and maraviroc	Pyrimidinediones
	Diterpene	Pyrimidinediones and ISIS 5320
	HHA, KRV2110, T20 combinations	siRNA
	KP1, KP17	SJ-3991
	LNG and MIV-150 in a vaginal ring	UC-781 and KP17
	mapp66 (combination of anti-CCR5 and anti-HSV antibodies)	UC-781 and progestin
		UC-781 and tenofovir
	Maraviroc and tenofovir	x-REPLAB
	MIV-150, zinc acetate, and carrageenan (carrageenan is an excipient)	Zinc acetate and MIV-150 in a vaginal ring
		Zinc tetra-ascorbo-camphorate derivative "C14"
	NCp7 Thioesters (SAMTs)	
	Nisin	
	Novasomes	
Novel and uncharacterised mechanisms	BASANT	Zinc acetate and carrageenan
	C5A (virucide)	Zinc

Obstacles to microbicide development

Funding

Several obstacles continue to hamper the development of a safe and effective microbicide. Financial commitments have been one of the biggest obstacles. In 2010, the total global investment for microbicide

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

research and development was US$247 million, with the public sector providing 93% of the funds. This is compared to funding of $859 million for HIV vaccine-related research and development in the same year: 3.5 times more than microbicides.[60] This huge discrepancy is largely because it has been difficult to mobilise pharmaceutical industry support for microbicide research; none of the major pharmaceutical companies have a substantive microbicide research and development portfolio, and none are conducting human microbicide trials at present. The reluctance to invest in microbicide development centres on their concerns about scientific and regulatory uncertainty and competing opportunities to invest in products that are potentially more profitable. Although funding of microbicide research has significantly increased over the years, a successful product will require extensive and sustained investment in research and development. The product pipeline in general needs a large number of products in phase I owing to the high attrition rate before a product warrants assessment for efficacy against HIV infection. At present, the dearth of products in the phase I pipeline is a source of major concern.

Validated animal model

Several animal models are used in pre-clinical microbicide testing (e.g. the mouse HSV-2 model, the rabbit vaginal irritation index), and the nonhuman primate (NHP) model. The predominant model being used is the simian immunodeficiency virus and the simian HIV challenge in NHPs, but the biological relevance of this model remains contentious.[43] Owing to the substantial differences in the human and primate vaginas (e.g. the primate vagina is neutral pH, whereas the human vagina has a low pH), it is unclear whether the NHP model accurately predicts what would occur in humans. For example, despite 0.5% PRO 2000® showing potent activity against HIV *in vitro*[25,61,62] and in animal models for vaginal HIV transmission,[63,64] human studies show that, although safe, 0.5% PRO 2000® gel may have little or no effect on reducing a woman's risk of HIV infection.[14,42] The absence of a validated animal model is a major obstacle to microbicide development, as it means that costly and time consuming human studies are required to assess any effect of a microbicide candidate.

Correlates of protection

Microbicide development has the distinct challenge of not having a precedent to emulate (e.g. HIV vaccine development can follow previous successful strategies used to develop vaccines against other viruses). Currently, no markers exist for the biological activity of microbicides and no markers have been established as correlates of protection for microbicides. One analysis has suggested a 1000 ng/ml drug concentration of tenofovir as a potential correlate of protection,[65] but this needs to be prospectively assessed. This obstacle presents a major impediment to rapid progress in the field, as HIV infection in humans is the key marker of biological activity, safety and efficacy. This means that meaningful studies of safety and efficacy of a microbicide can only be designed with HIV infection as the primary end point.

Ethical and logistical issues

Several logistical and ethical issues are involved in the conduct of microbicide trials. To show safety and efficacy, the product must be tested on large numbers of sexually active people. Trials also need to be conducted among selected populations that are likely to be at high risk of acquiring HIV infection. Clinical trials are thus often carried out either in developing countries that have high levels of infection.[66] This has raised concerns about the potential for exploitation of vulnerable populations; a concern that is, fortunately, not borne out of reality owing to the high ethical and care standards maintained in all the current microbicide trials. In addition, microbicide trials are, in reality, being conducted in many countries throughout the world, including Europe and the USA.

Counselling on use and provision of condoms as a proven HIV prevention method, in addition to the experimental product, is an ethical and moral pre-requisite in all HIV prevention trials, including microbicide trials. Under these conditions, the trial can only measure whether microbicides improve upon the protection afforded by condom use. Microbicides will also only work if they are widely accepted and used consistently by women. Other practical, ethical and scientific challenges that

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

complicate microbicide trial data include behaviours such as anal sex and the use of other intravaginal substances.

Other concerns surrounding the development of microbicide include the potential hazards related to reproductive toxicity and the increased risk of local toxicity from applying a product repeatedly to the same tissue, which may have long-term effects that could enhance risk of infection. Studies are under way to establish the safety of microbicide use during pregnancy. The threshold of acceptability, toxicity and efficacy will differ between countries, and those with an aggressive spreading disease, such as developing countries, may be more likely to accept a partially effective product.

Resistance

Some challenges unique to antiretroviral products being developed as candidate microbicides are concerns about the potential for development of drug resistance. Although resistance cannot develop in people who do not have HIV, it could possibly develop if the person taking the prophylactic regimen becomes infected with HIV while continuing to take the drugs. The contribution of acquired resistance from prophylactic use of antiretrovirals is estimated to be a much smaller contributor to drug resistance than the use of antiretrovirals in treatment.[67] Fortunately, to date, the studies investigating tenofovir as prevention have not detected any tenofovir resistance.[31,68]

Adherence

Adherence to the prescribed treatment or prophylactic regimen is critical. Suboptimal adherence will result in substantially lower effectiveness than that observed in the clinical trials. Evidence from the CAPRISA 004 trial[31] clearly demonstrates how effectiveness can be eroded with inconsistent use. In CAPRISA 004, although overall effectiveness was 39%, women who used the gel most consistently (gel adherence greater than 80%) had a 54% lower HIV incidence compared with women using the placebo.[31] Experiences from implementing antiretroviral therapy for AIDS treatment have shown that high levels of adherence are achievable in a real world setting, even in developing countries.[69–71] Although this is encouraging, this may not be readily applicable to adherence in asymptomatic healthy people. On the other hand, a highly effective product and understanding of HIV risk may serve as an incentive to use microbicides consistently. Suboptimal adherence could also exacerbate drug resistance.

Behavioural disinhibition

A concern when introducing new prevention technologies is that people may stop using a more efficacious HIV prevention method (e.g. condoms) for a less efficacious one (e.g. a partially effective microbicide).[72] This concern, commonly known as risk compensation or behavioural disinhibition, could potentially undermine and even reverse the beneficial effects of microbicides.[73] Although a low-efficacy intervention may be reversed by behavioural disinhibition, current evidence from medical male circumcision implementation has found this concern to be baseless. An assessment of the real-world effect of the roll-out of medical male circumcision in a community in South Africa has shown no evidence of risk compensation after 3 years.[74] Furthermore, no significant behavioural disinhibition was observed in the CAPRISA 004 trial.[31]

Conclusion

A women-controlled method to prevent HIV infection is urgently needed. Substantial progress has been made in the microbicide development field and, for the first time, the field is optimistic. There is now proof that a safe and effective microbicide, in the form of tenofovir gel, is possible. Despite numerous scientific, ethical, methodological, and implementation challenges, microbicides provide real potential to influence the course of the HIV epidemic, as they fill an important gap for women-initiated prevention methods.

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

Practice points

- A women-controlled method to prevent HIV infection is urgently needed.
- Proof is now available that a safe and effective microbicide, in the form of tenofovir gel, is possible.
- Microbicides provide real potential to influence the course of the HIV epidemic, as they fill an important gap for women-initiated prevention methods.

Research agenda

- The future microbicide development pipeline is likely to focus on finding a more efficacious microbicide product, dosing strategy and formulation than that observed with coitally related use of tenofovir gel.
- Combination products and combination approaches are seen as offering a potential for synergy, reduced drug resistance, and multiple targeting.
- Research on rectal microbicides is also likely to expand.

References

1. AIDS Epidemic Update. In: *Joint United Nations Programme on HIV/AIDS and World Health Organisation*. Geneva: UNAIDS, WHO, 2009.
2. Pettifor AE, Rees HV, Kleinschmidt I et al. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *Aids* 2005; **19:** 1525–1534.
3. Shisana O, Rehle T, Simbayi LC et al. *South African national HIV prevalence, incidence, behaviour and communication survey 2008: A turning tide among teenagers?*. Cape Town: HSRC Press, 2009.
4. Haynes BF & Shattock RJ. Critical issues in mucosal immunity for HIV-1 vaccine development. *J Allergy Clin Immunol* 2008; **122:** 3–9.
5. Yeaman GR, Asin S, Weldon S et al. Chemokine receptor expression in the human ectocervix: implications for infection by the human immunodeficiency virus-type I. *Immunology* 2004; **113:** 524–533.
6. Shattock RJ & Moore JP. Inhibiting sexual transmission of HIV-1 infection. *Nat Rev Microbiol* 2003; **1:** 25–34.
7. Abdool Karim Q. Heterosexual transmission of HIV – the importance of a gendered perspective in HIV prevention. In Abdool Karim SS & Abdool Karim Q (eds.). *HIV/AIDS in South Africa*. Cape Town: Cambridge University Press, 2005, pp. 243–461.
8. Gregson S, Nyamukapa CA, Garnett GP et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet* 2002; **359:** 1896–1903.
9. Abdool Karim Q, Abdool Karim SS & Nkomokazi J. Sexual behaviour and knowledge of AIDS among urban black mothers. Implications for AIDS intervention programmes. *S Afr Med J* 1991; **80:** 340–343.
10. Simbayi LC, Chauveau J & Shisana O. Behavioural responses of South African youth to the HIV/AIDS epidemic: a nationwide survey. *AIDS Care* 2004; **16:** 605–618.
11. Hoffman S, O'Sullivan LF, Harrison A et al. HIV risk behaviors and the context of sexual coercion in young adults' sexual interactions: results from a diary study in rural South Africa. *Sex Transm Dis* 2006; **33:** 52–58.
12. Jewkes RK, Levin JB & Penn-Kekana LA. Gender inequalities, intimate partner violence and HIV preventive practices: findings of a South African cross-sectional study. *Soc Sci Med* 2003; **56:** 125–134.
13. Gupta GR, Weiss E & Whelan D. Male-female inequalities result in submission to high-risk sex in many societies. Special report: women and HIV. *AIDS Anal Afr* 1995; **5:** 8–9.

*14. Abdool Karim SS, Richardson B, Ramjee G et al. Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women. *AIDS* 2010; **25:** 957–966.

15. Lagenaur LA, Sanders-Beer BE, Brichacek B et al. Prevention of vaginal SHIV transmission in macaques by a live recombinant Lactobacillus. *Nature* 2011; **4:** 648–657.
16. Richardson BA, Lavreys L, Martin Jr. HL et al. Evaluation of a low-dose nonoxynol-9 gel for the prevention of sexually transmitted diseases: a randomized clinical trial. *Sex Transm Infect* 2001; **28:** 394–400.
17. Kreiss J, Ngugi E, Holmes K et al. Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *Jama* 1992; **268:** 477–482.

*18. Roddy RE, Zekeng L, Ryan KA et al. A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. *N Engl J Med* 1998; **339:** 504–510.

*19. van Damme L, Ramjee G, Alary M et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360:** 971–977.

*20. Feldblum P, Adeiga A, Bakare R et al. SAVVY vaginal gel (C31G) for prevention of HIV infection: A randomized controlled trial in Nigeria. *PLoS One* 2008; **3:** e1471.

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

*21. Peterson L, Nanda K, Opoku BK et al. SAVVY® (C31G) gel for prevention of HIV infection in women: A phase 3, double-blind, randomized, placebo-controlled trial in Ghana. *PLoS One* 2007; **2:** e1312.
22. Pearce-Pratt R & Phillips D. Sulfated polysaccharides inhibit lymphocyte-to-epithelial transmission of human immunodeficiency virus-1. *Biol Reprod* 1996; **54:** 173–182.
23. Saifuddin M, Doncel G, Tsai L et al. Intravaginal administration of 6% cellulose sulfate (CS) gel prevented systemic infection in rhesus macaques in a multiple dose R5/X4 SHIV vaginal challenge model. In: *Microbicides 2008* February 24–27; 2008. Delhi, India.
24. Rusconi S, Moonis M, Merrill DP et al. Naphthalene sulfonate polymers with CD4-blocking and anti-human immunodeficiency virus type 1 activities. *Antimicrob Agents Chemother* 1996; **40:** 234–236.
25. Scordi-Bello I, Mosoian A, He C et al. Candidate sulfonated and sulfated topical microbicides: comparison of anti-human immunodeficiency virus activities and mechanisms of action. *Antimicrob Agents Chemother* 2005; **49:** 3607–3615.
26. Lewis M, Wagner W, Yalley-Ogunro J et al. Efficacy of PRO 2000 gel in a macaque model for vaginal HIV transmission [Abstract A-191]. In: *Microbicides 2002* 2002. Antwerp, Belgium.
27. Investigator's brochure: Sodium cellulose sulfate 6% vaginal gel. 2006.
28. Nunez M & Soriano V. Management of patients co-infected with hepatitis B virus and HIV. *Lancet Infect Dis* 2005; **5:** 374–382.
*29. Skoler-Karpoff S, Ramjee G, Ahmed K et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2008; **372:** 1977–1987.
30. Van Damme L, Govinden R, Mirembe FM et al. Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission. *New Engl J Med* 2008; **359:** 463–472.
*31. Abdool Karim Q, Abdool Karim SS, Frohlich JA et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 2010; **329:** 1168–1174.
32. Lederman M, Veazey RS, Offord R et al. Prevention of vaginal SHIV transmission in rhesus macaques through inhibition of CCR5. *Science* 2004; **306:** 485–487.
33. Marozsan AJ, Kuhmann SE, Morgan T et al. Generation and properties of a human immunodeficiancy virus type 1 isolate resistant to the small molecule CCR5 inhibitor, SCH-417690. *Virology* 2005; **338:** 182–199.
34. Gustchina E, Hummer G, Bewley CA et al. Differential inhibition of HIV-1 and SIV envelope-mediated cell fusion by C34 peptides derived from the C-terminual Heptad repeat of gp41 from diverse strains of HIV-1, HIV-2, and SIV. *J Med Chem* 2005; **48:** 3036–3040.
35. Voeller B. AIDS and heterosexual anal intercourse. *Arch Sex Behav* 1991; **20:** 233–276.
36. Gross M, Holte SE, Marmor M et al. Anal sex among HIV-seronegative women at high risk of HIV exposure. *JAIDS* 2000; **24:** 393–398.
37. Halperin DT. Heterosexual anal intercourse: prevalence, cultural factors, and HIV infection and other health risks, part I. *AIDS Patient Care* 1999; **13:** 717–730.
38. Kalichman SC, Simbayi LC, Cain D et al. Heterosexual anal intercourse among community and clinical settings in Cape Town, South Africa. *Sex Transm Infect* 2009; **85:** 411–415.
39. Schwandt M, Morris C, Ferguson A et al. Anal and dry sex in commercial sex work, and relation to risk for sexually transmitted infections and HIV in Meru, Kenya. *Sex Transm Infect* 2006; **82:** 392–396.
40. Smith AD, Tapsoba P, Peshu N et al. Men who have sex with men and HIV/AIDS in sub-Saharan Africa. *Lancet* 2009; **374:** 416–422.
41. Stein ZA. HIV prevention: the need for methods women can use. *Am J Publ Health* 1990; **80**(Issue)**:** 460–462.
*42. McCormack S, Ramjee G, Kamali A et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. 2010. *Lancet* 2010; **376:** 1329–1337.
43. Stone A & Harrison PF. *Microbicides – ways forward*. Silver Spring, MD, USA: Alliance for Microbicide Development, 2010.
44. De Clercq E. Acyclic nucleoside phosphonates: past, present and future. Bridging chemistry to HIV, HBV, HCV, HPV, adeno-, herpes-, and poxvirus infections: the phosphonate bridge. *Biochem Pharmacol* 2007; **73:** 911–922.
*45. Rohan LC, Moncla BJ, Kunjara Na Ayudhya RP et al. In vitro and ex vivo testing of tenofovir shows it is effective as an HIV-1 microbicide. *PLoS ONE* 2010; **5:** e9310.
46. National Institute of Allergy and Infectious Diseases (NIAID). *Safety and Effectiveness of Tenofovir 1% Gel, Tenofovir Disproxil Fumarate, and Emtricitabine/Tenofovir Disoproxil Fumarate Tablets in Preventing HIV in Women* 2011, http://clinicaltrials.gov/ct2/show/NCT00705679 [last accessed 30.01.12].
47. Microbicide Trials Network. *MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women* 2011, http://www.mtnstopshiv.org/node/3909 [last accessed 25.11.11].
48. Microbicide Trials Network. *Microbicide Trials Network Statement on Decision to Discontinue Use of Oral Tenofovir Tablets in VOICE, a Major HIV Prevention Study in Women* 2011, http://www.mtnstopshiv.org/node/3619 [last accessed 1.11.11].
49. CONRAD. *Safety and Effectiveness of Tenofovir Gel in the Prevention of Human Immunodeficiency Virus (HIV-1) Infection in Young Women and the Effects of Tenofovir Gel on the Incidence of Herpes Simplex Virus (HSV-2) Infection* 2011, http://clinicaltrials.gov/ct2/show/NCT01386294 [last accessed 30.01.12].
50. Williams BG, Abdool Karim SS, Gouws E et al. Potential impact of tenofovir gel on the HIV epidemic in South Africa. *J Acquir Immune Defic Syndr* 2011; **58:** 207–210.
51. National Institute of Allergy and Infectious Diseases (NIAID). *Safety of Acidform Lubricant in HIV-Uninfected Women* 2009, http://clinicaltrials.gov/ct2/show/NCT00850837 [last accessed 30.01.12].
52. AVAC –; Global Advocacy for HIV prevention. Tables on ongoing and planned clinical trials; http://www.avac.org/ht/d/sp/i/3512/pid/3512 [last accessed 26.01.12].
53. International Partnership for Microbicides. *A Safety Study of Dapivirine Vaginal Ring in Africa* 2010, http://www.clinicaltrials.gov/ct2/show/NCT01071174 [last accessed 30.01.12].
54. International Partnership for Microbicides. *Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women* 2009, http://clinicaltrials.gov/ct2/show/NCT00917904 [last accessed 30.01.12].
55. International Partnership for Microbicides. *A Safety Study of Two Dapivirine (TMC120) Vaginal Gels in the United States* 2008, http://clinicaltrials.gov/ct2/show/NCT00799058 [last accessed 30.01.12].

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010

56. International Partnership for Microbicides. *Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures* 2011, http://clinicaltrials.gov/ct2/show/NCT01277640 [last accessed 30.01.12].
57. International Partnership for Microbicides. *Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring* 2011, http://clinicaltrials.gov/ct2/show/NCT01363037 [last accessed 30.01.11].
58. CONRAD. *Rectal Safety and Acceptability Study of Tenofovir 1% Gel* 2010, http://clinicaltrials.gov/ct2/show/NCT01232803 [last accessed 30.01.12].
59. CONRAD. *Microbicide Safety and Acceptability in Young Men (Project Gel)* 2011, http://clinicaltrials.gov/ct2/show/NCT01283360 [last accessed 30.01.12].
60. The HIV Vaccines and Microbicides Resource Tracking Working Group. *Capitalizing on Scientific Progress: Investment in HIV Prevention R&D in 2010*. 2011; Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/pressrelease/2011/07/20110719_RTWG_Capitalizing_Scientific_Progress.pdf [last accessed 26.01.12].
61. Dezzutti CS, James VN, Ramos A et al. In vitro comparison of topical microbicides for prevention of human immunodeficiency virus type 1 transmission. *Antimicrob Agents Chemother* 2004; **48:** 3834–3844.
62. Greenhead P, Hayes P, Watts PS et al. Parameters of human immunodeficiency virus infection of human cervical tissue and inhibition by vaginal virucides. *J Virol* 2000; **74:** 5577–5586.
63. Lewis MG, Wagner W, Yalley-Ogunro J et al. Efficacy of PRO 2000 Gel in a macaque model for vaginal HIV transmission. [Abstract A-191]. In: *Microbicides 2002* 2002. Antwerp, Belgium.
64. Weber J, Nunn A, O'Connor T et al. 'Chemical condoms' for the prevention of HIV infection: evaluation of novel agents against SHIV(89.6PD) in vitro and in vivo. *AIDS* 2001; **15:** 1563–1568.
65. Abdool Karim SS, Kashuba A, Werner L et al. Drug concentrations following topical and oral antiretroviral pre-exposure prophylaxis: Implications for HIV prevention in women. *Lancet* 2011; **378:** 279–281.
66. Abdool Karim SS & Baxter C. Chapter 16: New prevention strategies under development/investigation. In Abdool Karim SS & Abdool Karim Q (eds.). *HIV/AIDS in South Africa*. 2nd ed. Cape Town: Cambridge University Press, 2010, pp. 268–282.
67. Abbas U, Glaubius R, Mubayi A et al. Predicting the Impact of ART and PrEP with Overlapping Regimens on HIV Transmission and Drug Resistance in South Africa [abstract #98LB]. In: *18th Conference on Retroviruses and Opportunistic Infections* 2011. Boston, Massachusetts.
*68. Grant RM, Lama JR, Anderson PL et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–2599.
69. van Oosterhout JJ, Bodasing N, Kumwenda JJ et al. Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. *Trop Med Int Health* 2005; **10:** 464–470.
70. Nachega JB, Stein DM, Lehman DA et al. Adherence to Antiretroviral Therapy in HIV-Infected Adults in Soweto, South Africa. *AIDS Res Hum Retrovir* 2004; **20:** 1053–1056.
71. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA et al. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. *Int J STD & AIDS* 2005; **16:** 38–41.
72. Cassell MM, Halperin DT, Shelton JD et al. Risk compensation: the Achilles' heel of innovations in HIV prevention? *Br Med J* 2006; **332:** 605–607.
73. Vissers DC, Voeten HA, Nagelkerke NJ et al. The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. *PLoS ONE* 2008; **3:** e2077.
74. Auvert B, Taljaard D, Rech D et al. Effect of the Orange Farm (South Africa) male circumcision roll-out (ANRS-12126) on the spread of HIV [abstract WELBC02]. In: *Sixth International AIDS Society conference* 2011. Rome.

Please cite this article in press as: Abdool Karim SS, Baxter C, Overview of microbicides for the prevention of human immunodeficiency virus, Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.01.010